Peer Review
Experimental Toxicology Division
N H E E R L

CUMULATIVE RISK

Evaluating the TEF Methodology for Cumulative Risk for Dioxins

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1UNC-CH Curriculum in Toxicology

INTRODUCTION

Dioxins are one of the first class of chemicals that the USEPA evaluated for cumulative risk. Dioxins are a class of chemicals that exert their toxicity through binding to the Ah receptor. The most potent of these chemicals is 2,3,7,8-tetrachlorodibenzo-p-dioxin. Exposure to dioxins occurs as part of a complex mixture. In 1987 an expert panel assembled by the USEPA recommended the use of the Toxic Equivalency Factor (TEF) methodology as an interim risk assessment tool to estimate potential health effects of exposure to dioxin-like chemicals. More recently, an international panel has also recommended the use of the TEF not only for human health risk assessments but also for ecological risk assessments (Van den Berg et al 1998).

There are a number of assumptions and uncertainties in the TEF methodology:

1. The toxicity of all chemicals included in the TEF methodology is mediated by the Ah receptor.
2. The relative potency of a chemical is equivalent across all endpoints.
3. The relative potency of a chemical is equivalent across all species
4. The relative potency of a chemical is equivalent across exposure scenarios.
5. The chemicals interact in a dose additive manner.

Research in ETD has focused on examining several of these assumptions in order to better characterize the uncertainty in the use of the TEF method.

Study goals

Project: 1

1. To determine if the REPs are equivalent across endpoints in a single species
2. To determine if mixtures of dioxins act in a dose additive manner
3. To determine if REPs from mice can predict responses in rats.

Project 2

To determine if the WHO TEFs can predict responses of a laboratory defined mixture

Project 3

1. To determine if the WHO TEFs can predict responses in Aroclor 1254 mixtures

Project 1

Materials and Methods

Single chemical studies

Female B6C3F1 mice were exposed 5 days/week for 13 weeks to individual PHAHs (Table 1) and killed 3 days after the last exposure. Endpoints examined are in Table 2. Relative potencies were determined using the method of DeVito et al (1997).

Mixture Study

A mixture of PCDDs, PCDFs and PCBs were prepared based on relative environmental occurrence and human exposure (Table 1). Mice and rats were exposed to this mixture by oral gavage 5 days/week for 13 weeks and killed 3 days after the last exposure. The endpoints examined are in Table 2

Table 1
Chemicals and mixtures tested

Chemical	Ratio to TCDD	REP	TEQ	%TEQ
TCDD	1	1	1	40.7
PeCDD	1	.67	.67	29.9
TCDF	1.5	.031	.047	2.1
1-PeCDF	0.5	0.12	0.006	<1
4-PeCDF	2	0.22	0.44	19.6
OCDF	5	$9.3x10^{-5}$	$4.7x10^{-4}$	<1
PCB 77	150	$6.0x10^{-5}$	0.009	<1
PCB 126	45	0.011-0.0059	0.05-0.27	3-12
PCB 169	30	$2.5x10^{-4}$	0.0075	<1
PCB 105	6000	$2.2x10^{-6}$	0.013	<1
PCB 118	30000	$9.3x10^{-7}$	0.0028	<1
PCB 156	1000	$1.3x10^{-6}$	.0013	<1

Table 2
Endpoints examined

Mice and Rats	Mice	Rats
EROD Liver Lung Hepatic Retinoids	EROD Skin Immunotoxicity PFC response to SRBC Hepatic Porphyrins PHAH Tissue concentrations	Serum thyroid hormones

Project 1

Results

REPs varied less than 5 fold for each chemical across endpoints

For most chemicals, the REPS did not differ by more than a factor of 2 when comparing administered dose vs. tissue concentrations.

The REP for 4-PeCDF was significantly different (greater than 10 fold) when derived based on administered dose or tissue concentration.

Using REPs based on hepatic EROD induction provides good predictions of enzyme induction in liver lung and skin for a mixture of PCDDS/PCDFs and PCBs (figures 1-3).

Using REPs based on hepatic EROD induction provides reasonable predictions of the immunotoxicity of the mixture in mice (Figure 4).

REPs based on hepatic EROD in slightly under predict hepatic EROD induction of the mixture in rats.

REPs based on hepatic EROD in mice significantly under predict the dose response relationship of the mixture for decreases in serum thryoxine in rats

Figure 1

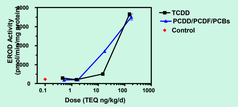


Figure 2

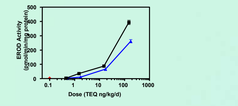


Figure 3

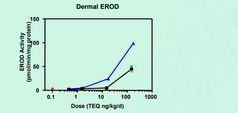


Figure 4

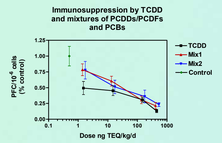


Figure 5

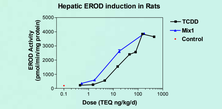
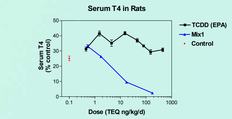


Figure 6



Project 2

Methods

Female Long Evans rats were received a single exposure of either TCDD or a mixture of dioxins (Table 3) on GD 15. Organ weights, markers of puberty and sperm counts were examined.

Dose is described as either TCDD or TEQ ng/kg based on WHO TEF values.

Table 3

Chemical	TEF	Ratio	% TEQ
TCDD	1	1	12.5
PCDD	1	1	12.5
TCDF	0.1	1.5	2
1-PeCDF	0.05	.5	<1
4-PeCDF	0.5	2	12.5
OCDF	0.0001	5	<1
PCB 77	0.0001	150	<1
PCB 126	0.1	45	56
PCB 169	0.01	30	4

Results

The TEF methodology under predicted some the markers of toxicity of the mixture compared to TCDD (Figure 7) and did well predicting other effects (Figure 8).

Figure 7

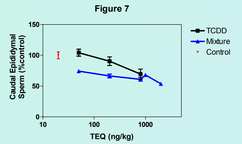
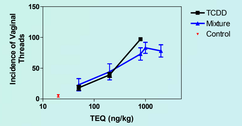


Figure 8



Project 3

Materials and Methods

Two different lots of Aroclor 1254 that differ in dioxins equivalents by 10 fold were administered were administered to Long Evans Rats and killed 4 days later.

Lot 6024 is 400 ppm TEQ
Lot 124-191 is 39 ppm TEQ

Hepatic EROD and serum thryoxine were determined.

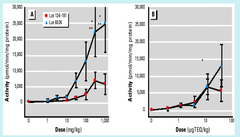
Dose response analysis was performed based on total PCB dose (mg/kg) or on TEQ based on the WHO TEF values.

Results

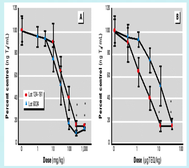
The TEF methodology accurately predicts the dose response relationship for increases in hepatic EROD activity of the two mixtures

The TEF methodology does not predict the dose response relationships for decreases in serum thyroxine.

Dose response relationship for hepatic EROD by different lots of Aroclor 1254 based on total dose (A) and TEQ dose (B)



Dose response relationship for decreases in serum thyroxine by different lots of Aroclor 1254 based on total dose (A) and TEQ dose (B)



Conclusions:

The TEF methodology provides a reasonable approximation of the toxic effects of a mixture of dioxin-like chemicals. With the following caveats:

The predictions are best for effects strictly mediated by the Ah receptor (enzyme induction).

Effects that occur through multiple pathways maybe under predicted the response (thyroid hormones).

A separate set of TEF values for administered dose and tissue concentrations may be of value in applying this methodology.

Impact

This work provides some insight into the uncertainty of the TEF methodology and may allow risk assessors to better use this method.

Future Directions

We have no future efforts in this area at this time

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